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Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

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Thirty-eight patients with locally advanced breast cancer (Stage III) were treated over a 3-year period. All patients initially received two cycles of CMF (cyclophosphamide, 100 mg/m^2 p.o. d1–14; methotrexate 40mg/m^2 intravenously (iv), d1 and d8., 5 Fluorouracil 500 mg/m^2 iv d1 and d8). They were then subjected to surgery and external beam irradiation to the chest field and drainage areas. Four more cycles of chemotherapy completed the treatment protocol. A response to initial chemotherapy was seen in 75.7% patients, with two patients achieving a complete response. No patient had disease progression while on chemotherapy. Tumor reduction of a degree to allow breast conservation procedures was seen in eight patients. The chemotherapy was well tolerated. Twelve patients failed to complete the treatment protocol. Follow-up for the remaining 26 ranges from 9–40 months (mean 18 months). Ten patients developed a recurrence. Of those, only one had isolated local recurrence, two had local and systemic recurrence, and seven had systemic disease alone. Patients with recurrence were salvaged with further chemotherapy (Adriamycin and cyclophosphamide).

KEY WORDS: **neoadjuvant chemotherapy, breast cancer**

INTRODUCTION

Notwithstanding increased public awareness and an increased use of screening mammography, ~20% of all patients with breast cancer in the United States have locally advanced disease [1]. In India, a multitude of reasons in addition to public ignorance, such as economic circumstances and lack of access to medical facilities, bring the patient to the clinician at a relatively advanced stage. The difficulties in the management of locally advanced breast cancer (LABC) were brought out in 1943 by Haagensen and Stout [2] in their retrospective review of such patients treated by radical mastectomy alone. The 5-year local recurrence rate was 48% and the 5-year disease-free survival only 3%, all patients eventually dying of metastatic disease [2]. For this reason, many clinicians approach the treatment of LABC with "palliative" intent.

The poor results obtained with surgery alone led to the incorporation of radiotherapy in the treatment of LABC. Preoperative radiation therapy followed by surgery achieved local control in the range of 11–45%, but metastases developed subsequently in 65–89%. Surgery followed by radiotherapy achieved better results with local control in 70–86% [3]. The last two decades have established the contribution of adjuvant chemotherapy in the management of breast cancer by reducing the odds of recurrence and death [4]. It is no surprise that chemotherapy has been included in the treatment in LABC because the major failure was the occurrence of systemic disease.

With the use of surgery and radiotherapy to eradicate local disease and chemotherapy to eradicate micrometastatic disease, "potentially curative" treatment of LABC became possible. When it became apparent that combination chemotherapy could produce major tumor reductions, chemotherapy became the starting point of this therapy. First reported by De Lena from Milan [5], this has become accepted as the standard form of treating LABC.

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TABLE I. Locally Advanced Breast Cancer: Treatment Plan

A. Chemotherapy—2 cycles
B. Surgery
C. Radiotherapy
D. Chemotherapy—4 cycles

We present our initial experience of induction chemotherapy and multimodality treatment in patients with LABC.

MATERIALS AND METHODS

Between January 1991 and December 1993, patients with stage III breast carcinoma were treated by a single surgeon (GS) at the Nehru Hospital, PGIMER, Chandigarh. All patients had histologic proof of breast carcinoma and were clinically staged according to the AJC-UICC TNM classification [6]. Patients >60 years were not accepted for the treatment schedule. All patients were initially examined by a surgeon. In addition to a complete physical examination, the initial evaluation included complete blood counts, chest X-ray, liver biochemistry and ultrasound, bone scan, and skeletal survey to rule out metastatic disease. Patients with inflammatory carcinoma were excluded.

The treatment plan is illustrated in Table I. Initial chemotherapy consisted of 5-fluorouracil (500 mg/m^2 intravenously (iv) on days 1 and 8), methotrexate (40 mg/m^2 iv on days 1 and 8), and cyclophosphamide (100 mg/m^2 p.o. on days 1 through 14) in 28-day cycles. Response to induction chemotherapy was assessed by physical examination at the end of two cycles. Standard criteria for tumor regression were used to classify response [7].

The subsequent surgical treatment was based on the amount of residual tumour and usually consisted of a radical or modified radical mastectomy. If tumor regression made breast conservation feasible, it was performed.

All patients underwent external beam irradiation using cobalt teletherapy unit at 80 cm SSD or a 6 mV linear accelerator at 100 cm SSD. The radiation portals consisted of tangential chest fields for chest wall or intact breast using 15–30° wedge filters as compensators. The drainage area was treated through separate fields using one for internal mammary nodes and other for supraclavicular and axillary region. After completion of radiation, the patients received another four cycles of the same chemotherapy regimen.

During the administration of chemotherapy, the blood counts were monitored every 15 days. Chemotherapy was temporarily withheld if the white blood cell (WBC) counts dropped below 3.5 × 10^9/L or the platelet counts below 80 × 10^9/L. All toxicities were recorded and graded according to the WHO classification [7].

Follow-up of patients was performed at 3-month intervals after completion of therapy. One year following diagnosis, the patients were reinvestigated to look for evidence of metastases.

TABLE II. Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer: Toxicity

	Grades 1 and 2	Grades 3 and 4	Total
1. Nausea and vomiting	10 (30.3%)	2 (6.06%)	12 (36.4%)
2. Diarrhea	5 (15.2%)	—	5 (15.2%)
3. Alopecia	20 (60.6%)	3 (9.09%)	23 (69.7%)
4. Leucopenia	8 (24.2%)	—	8 (24.2%)

RESULTS

Thirty-eight female patients with locally advanced breast cancer (LABC) were enrolled in the treatment protocol. The patients were aged from 28 to 60 years (median 45 years). There was one patient with a 3 cm tumor with very large fixed nodes in the axilla (T_2N_2). Three patients had a local tumor excision done elsewhere and presented to us 6 months, 8 months, and 1 year later with massive disease in the axilla alone (T_XN_2). The remaining 34 patients had T_{3-4} N_{1-2} tumors. All patients had invasive ductal carcinoma.

Response to Chemotherapy

Five patients did not complete the first two cycles of chemotherapy. The overall objective response was 75.7%. Two patients (6.01%) achieved a complete response, 23 patients (69.7%) achieved a partial response, and 8 patients (24.3%) showed no change. Disease progression was not observed in any patient while on chemotherapy.

Side Effects

Chemotherapy was generally well tolerated. Alopecia was the most common side effect, despite the fact that no Adriamycin was administered (Table II). Leukopenia was not a problem, and a count of 2.5 × 10^9/L was reached only once. No patients required hospitalization due to complications. There were no septic episodes and no antibiotics were administered.

Surgery

Five patients completed the induction chemotherapy but refused surgery and further treatment. Two patients who achieved a complete response were not subjected to surgery. The patient with a small primary and large axillary nodes achieved a complete response for the primary tumor and a major reduction in the nodal size. A partial response was achieved in the other three patients having T_X N_2 disease. All four of these patients underwent an isolated complete axillary dissection (up to level III). Two patients achieved a sufficient reduction to undergo lumpectomy and axillary clearance.

TABLE III. Locally Advanced Breast Cancer: Surgery Performed

Radical mastectomy	10	71.4%
Patey mastectomy	10	
Lumpectomy + axillary clearance	2	
Axillary clearance	4	28.6%
No surgery	2	

The remaining 20 patients required either a radical mastectomy (10 patients) or a Patey mastectomy (10 patients) to achieve tumor clearance. Breast conservation was possible in eight patients (28.6%) (Table III).

Radiotherapy

A median dose of 40Gy/4 weeks/20 fr, 200cGy/day, 5 days a week, was delivered to the 28 patients after the wounds had healed. All patients had grade I–II dysphagia by the end of the second week of irradiation due to radiation esophagitis. Skin reactions were minor. Irradiation was not interrupted due to adverse reactions in any patient.

Follow-Up

A further two patients were lost in follow-up after surgery and radiotherapy. Twenty-six patients completed the treatment protocol and had no residual disease at the end of treatment. These patients have been followed up for a mean duration of 18 months (range 9–40 months). Sixteen patients (61.5%) are alive and have no evidence of disease on follow-up. Ten patients (38.5%) have developed a recurrence at a mean interval of 15.8 months (range 9–24 months) from time of diagnosis. One patient had an isolated locoregional failure, two had locoregional and systemic disease, and seven had systemic disease only. Liver was the most common site of systemic disease (4 patients), followed by soft tissues (3 patients), bone and CNS (2 patients each), and lungs (1 patient).

Four patients did not attend the hospital after diagnosis of recurrent disease. Two patients presented to the hospital with metastatic disease and died soon after. The remaining four patients were treated with further chemotherapy (Adriamycin 50 mg/m^2 iv, and cyclophosphamide 800 mg/m^2 iv, repeated at 3-week intervals). One patient achieved a complete response and is doing well at present. One patient had a partial response and 10 months later developed intracranial metastases and died. Another patient had progressive disease while on chemotherapy and died 3 months later. The last patient is still receiving chemotherapy and has achieved a partial response.

Thus 17 patients (65.4%) are alive and have no evidence of disease at the time of analysis.

DISCUSSION

The treatment of choice for locally advanced breast carcinoma has developed from radiotherapy and/or surgery to a combination of systemic and regional therapies. This is best illustrated by seeing the results of treatment of LABC in a single institution over the last 30 years [8] (Table IV). The initial clinical trials involving the use of neoadjuvant or induction chemotherapy began in the mid-1970s. Since then, there have been multiple reports documenting the efficacy of chemotherapy in LABC and the subject has been reviewed extensively [9, 10].

TABLE IV. Effect of Different Forms of Treatment on Locally Advanced Breast Cancer in a Single Institution [8]

	Survival		
	5 yr	10 yr	Local control
Irradiation	19%	11%	31%
Irradiation + mastectomy	32%	19%	80%
Irradiation + chemotherapy	31%	10%	54%
Irradiation + mastectomy + chemotherapy	45%	36%	91%

The use of chemotherapy as the first therapeutic modality results in a substantial reduction in tumor volume in ~70% of patients. Using complex hormonal synchronization and prolonged chemotherapy, response rates of 90% have been achieved [11]. This tumor reduction makes inoperable tumors operable and also increases the chances of less radical surgery or breast preservation in case of a marked response [12]. It also provides an in vivo assessment of response and the possibility of altering therapy based on this response assessment. Micrometastases, which are the cause of poor survival in LABC, are targeted with the initial chemotherapy. There is no postsurgical growth spurt with the use of induction chemotherapy. An intact vasculature of the breast produces adequate tissue concentration of the drug and better response rates. However, a delay in the local treatment (surgery and/or irradiation), large tumor burden, and drug resistance are some of the limiting factors in the use of induction chemotherapy.

A literature review reveals that doxorubicin containing regimens are preferred because they induce a higher response rate in metastatic breast cancer than regimens that do not [13]. Unfortunately, the cost of doxorubicin-containing regimens in India is very high and out of the reach of most patients. We have chosen to use the standard CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) combination for induction chemotherapy, which is economical, and we have achieved a 75.7% overall response and a 6.0% complete response rate. A higher complete response rate could have been achieved if chemotherapy had been administered to the point of maximum objective clinical response. Knowing the high failure rate following treatment of LABC, it may be beneficial to keep doxorubicin in reserve, as it is difficult to know what to recommend when the tumor is no longer respon-

sive to doxorubicin. A similar approach has been advocated for disseminated breast cancer [14].

Surgery alone, radiotherapy alone, or a combination of both have been used for locoregional tumor control after induction chemotherapy. As expected, locoregional treatment does not appear to influence survival in these patients. However, it does seem that the highest local control is achieved by the use of both surgery and radiotherapy [10]. However, in case a complete tumor regression is achieved, surgery may be omitted and only radiotherapy given [11, 15]. Two of our patients who achieved a complete response received only external irradiation and continue to do well 16 months and 20 months, respectively, from diagnosis.

The use of both surgery and radiotherapy for local tumor control introduces the problem of which to use first. In contrast to the well-known effect of radiotherapy interfering in wound healing, preoperative chemotherapy has not been shown to have any ill effect on healing after mastectomy [16, 17]. A reported reduction in lymphorrea after mastectomy [17] was not observed by us in our patients. We did not see an increased incidence of flap necrosis or wound infection. Tumor debulking also may make it easier for radiotherapy to sterilize the field.

Continuation of adjuvant chemotherapy following radiotherapy appears logical as we have used a fixed cycle induction chemotherapy. We have chosen to continue with the same combination as we did not have disease progression on chemotherapy in any patient. We have limited the total number of cycles to six as it has been shown that the benefit with short-term chemotherapy is of the same order as with long-term chemotherapy [4].

A multimodality treatment of this kind is complex and involves repeated monitoring and visits to the hospital. It is not surprising that there were a lot of dropouts during treatment. The factors operative in causing a delay in diagnosis in our setup also influence the follow-up. We have reduced this dropout rate by explaining the protocol in detail to the patient in the beginning and stressing that this kind of treatment is essential. Fortunately, all patients completing the treatment protocol have reported back, at least until the first recurrence.

Although the mean follow-up is short, the local tumor control is very encouraging with only three patients having recurrent tumor locally after a mean follow-up of 18 months. The number of patients in the study is too small to permit analysis of subsets and factors influencing outcome. However, initial results are very encouraging and we are continuing with this study.

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